succinate results in lower local irritant effects as compared to other commonly used buffers, such as sodium acetate. See Example 5 and Figure 8. Applicants submit that one of skill in the art would not expect such results. Notwithstanding this evidence of unexpected results, the claims at issue herein are directed to pharmaceutical compositions comprising at least one pharmaceutically active agent and a buffer that consists substantially of succinate and a counterion.

The Rejections of the Claims under 35 U.S.C. §112, First Paragraph, Enablement, Should Be Withdrawn

Claims 1-14 and 21-34 are rejected under 35 U.S.C. §112, first paragraph. This rejection is respectfully traversed.

The specification need describe the invention only in such detail as to enable a person skilled in the most relevant art to make and use it. *In re Naquin*, 158 USPQ 317, 319 (C.C.P.A. 1968).

In the present application, the independent claims at issue, i.e., claims 1 and 21, are directed to pharmaceutical compositions comprising at least one pharmaceutically active agent and a buffer consisting substantially of succinate at a concentration of about 10 mM to about 40 mM and a counterion. Various dependent claims are directed to these compositions, wherein specific pH ranges, tonicifying agents, counterions, and pharmaceutically active agents are recited. The terms "succinate buffer" and "pharmaceutically active agents" are defined in the specification and examples are provided. See the specification at page 7, lines 7-16, and at page 8, lines 3-14. Suitable molarity ranges for the succinate compositions are provided. See the specification at page 7, line 7, through line 2 on page 8. Tonicifying agents and methods for determining the isotonicity of a solution are known to those skilled in the art. See the specification, page 16, line 5, through line 4 on page 17. Examples are provided describing the determination of the suitability of various formulations for a particular pharmaceutically active agent, i.e., IGF-1. See the specification, page 25, line 9, through line 11 on page

26. Further, as noted in the specification, methods for the formulation and selection of pharmaceutically acceptable carriers, stabilizers, etc., are discussed in *Remington's Pharmaceutical Sciences* (1990) (18th ed., Mack Pub. Co., Eaton, Pennsylvania) (specification, page 21, lines 21-24).

Given the guidance provided in the specification, one of skill in the art would be able to formulate the compositions claimed without undue experimentation. One of skill in the art would also know to administer the compositions as injectable pharmaceutical formulations. Thus, one of skill in the art would know how to make and use the claimed compositions. The claimed compositions are therefore enabled.

The Office Action states that "[t]he terminology 'succinate causes less pain on injection' which is critical or essential to the practice of the invention, but not included in the claim(s) is not enabled by the disclosure" and that "the critical feature(s) that were discovered by applicant are not cited in the claims." However, Applicants claims are directed to a composition, i.e., a buffering system utilizing succinate. While Applicants have discovered that the composition, when injected, causes less pain upon injection as compared with other buffering systems, this effect is an unexpected result of the composition. As such, the evidence is relevant to the nonobviousness inquiry under 35 U.S.C. §103, not the enablement inquiry of 35 U.S.C. §112.

In view of these remarks, Applicants respectfully request that this rejection of the claims be withdrawn.

The Rejections of the Claims under 35 U.S.C. §112, Second Paragraph, Should Be Withdrawn

Claims 1-14 and 21-34 are rejected under 35 U.S.C. §112, second paragraph. This rejection is respectfully traversed.

The legal standard of definiteness is whether a claim reasonably apprises those of skill in the art of its scope. *See In re Warmerdam*, 33 F.3d 1354, 31 USPQ2d 1754 (Fed. Cir. 1994). Furthermore, the claim must be read in light of the specification. *See, e.g., Credle v. Bond*, 25 F.3d 1566, 30 USPQ2d 1911 (Fed. Cir. 1994).

The Office Action states that the term "substantially" renders claims 1-14 and 21-34 indefinite. Although no further explanation is provided, Applicants respectfully submit that use of the term "substantially" has been upheld as definite in several cases. See MPEP §2173.05(b).

The Office Action further states that the terms "at least one" and "such that" render the claims indefinite. Again, no further explanation has been provided.

With respect to the term "at least one," Applicants note that open-ended numerical ranges are not necessarily indefinite. See MPEP §2173.05(c) II. The term "at least one," as used in claim 1, is directed to a formulation of "at least one pharmaceutically active agent and a buffer, wherein said buffer consists substantially of succinate at a concentration of about 10 mM to about 40 mM and a counterion." The specification states that pharmaceutically active agents include "any pharmaceutically effective compound that is compatible with succinate buffer" and provides examples of pharmaceutically active agents (page 8, paragraph 1). Applicants respectfully submit that, when read in light of the specification, one of skill in the art would be reasonably apprised of the scope of the invention as claimed.

Both "at least one" and "such that" appear in claims 9 and 29, which use identical language and depend from claim 1 and claim 21, respectively. As used in claim 9, for example, the terms are directed to "he composition of claim 1, further comprising a sufficient concentration of at least one tonicifying agent such that the composition is isotonic." The specification explains how to adjust a solution using a tonicifying agent "such that" it is isotonic (page 16, paragraph 1, to page 17, especially page 16, paragraph 1). Furthermore, "isotonic" is defined on page 16 of the specification. Examples of tonicifying agents are given, as well as references to methods known in the art for making a solution isotonic. Applicants respectfully submit that tonicifying agents are their use are well known in the art. See, e.g., *Remington's Pharmaceutical Sciences* (1990) (18th ed., Mack Pub. Co., Eaton, Pennsylvania). Applicants submit that the terms "at least one" and "such that" would be understood by one of skill in the art and would reasonably

apprise one of skill in the art of the scope of the claims. Accordingly, Applicants respectfully request that this rejection be withdrawn.

The Rejection of the Claims under 35 U.S.C. §103(a) Should Be Withdrawn

The rejection of the claims under 35 U.S.C. § 103(a) over the '620 patent in light of the '249 patent is maintained. In support of this rejection, the Examiner cites an additional reference, Acott *et al.*, United States Patent 5,985,830 (the "'830 patent"). This rejection is respectfully traversed.

The references cited by the Examiner, alone or in combination, do not teach or suggest the molarity range recited in Applicants' claimed invention. For instance, the '620 patent teaches IGF-1 and growth hormone in an acetic acid buffer. The '620 patent does not recite any concentration limitation for a succinate buffer, and only mentions succinate briefly in the following passage:

> Examples include acetic acid salt buffer, which is any salt of acetic acid, including sodium acetate and potassium acetate, succinate buffer, phosphate buffer, citrate buffer, or any others known to the art to have the desired effect. The most preferred buffer is sodium acetate, optionally in combination with sodium citrate.

('620 patent, column 8-14).

Similarly, the '830 patent teaches the preferred use of IGF-1 in an acetic acid buffer for the reduction of kidney cyst incidence and severity ('830 patent, column 7, lines 51-61). As noted in the Office Action, the '830 patent mentions succinate in a paragraph discussing carriers:

> The carrier suitably contains minor amounts of additives such as substances that enhance isotonicity and chemical stability. Such materials are non-toxic to recipients at the dosages and concentrations employed and include buffers such as phosphate, citrate, succinate, acetic acid, and other organic acids or their salts; antioxidants such as ascorbic acid; low molecular weight (less than about ten residues) polypeptides, e.g., polyarginine or tripeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as poly-vinylpyrrolidone; amino acids, such as glycine, glutamic acid, aspartic acid, or

> arginine; monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, mannose, or dextrins; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; counterions such as sodium; and/or nonionic surfactants such as polysorbates, poloxmers, or PEG.

('830 patent, column 6, line 66 to column 7, line 14). However, no concentration range for using succinate carriers is taught.

Finally, the '249 application discloses interferon in a 50 mM succinate buffer with a counterion. This concentration lies outside the molarity range for succinate as claimed by Applicants.

Thus, the references, alone or in combination, do not teach or suggest the molarity range recited in Applicants' claimed invention. Furthermore, both the '620 patent and '830 patent teach away from the use of succinate buffer, stating that the preferred buffer is sodium acetate or acetic acid (above). Consequently, a prima facie case of obviousness has not been established.

Moreover, Applicants have discovered and disclosed the unexpected result that succinate buffers within the claimed range limitation produce less pain on injection than other buffering systems. Applicants have disclosed data demonstrative of this result, as well (see Summary, above). Thus, within the specification, Applicants have asserted secondary evidence of nonobviousness.

In response, the Examiner cites the '830 patent for the use of IGF-1 to reduce kidney cyst incidence and/or severity, noting that "succinate is used in the composition." The Examiner then reasons that "reducing the kidney cyst incidence and/or severity is inherently accompanied by reducing pain and said pain reduction could also be inherent in the use of IGF-1, and not succinate."

Applicants' representative has diligently reviewed the '830 patent and has been unable to locate any disclosure regarding pain, or pain reduction, associated with the administration of IGF-1 in any buffer. In any case, even if reduction of kidney cyst incidence and/or severity is inherently accompanied by a reduction in pain, this would not demonstrate that one of skill in the art would expect the use of 10-40 mM succinate as a buffer to reduce pain on injection. Rather, the sort of pain reduction hypothesized by the Examiner would seem to accompany the

successful reduction of kidney cyst incidence. As noted by the Examiner, this sort of pain reduction would be inherent in the successful application of IGF-1 and would be unrelated to the painfulness of an injection. Thus, the reference relied upon by the Examiner does not rebut Applicants' evidence of secondary consideration of nonobviousness.

The Office Action also states that Applicants must demonstrate the criticality of the molarity range claimed by Applicant. There are cases supporting the requirement of such a demonstration where the range claimed by an applicant overlaps with or is encompassed by a range disclosed in the prior art. *See In re Geisler*, 43 USPQ2d 1362, 1365 (Fed. Cir. 1997) (applicant required to show that the claimed range is critical when range is within, or overlaps with, a range disclosed in the prior art); *In re Woodruff*, 16 USPQ2d 1934 (Fed. Cir. 1990) (applicant failed to support unexpected results by showing criticality of carbon monoxide range where that range overlapped with prior art range). These cases are distinguishable from the present case because neither the '830 or '620 patents disclose a molarity range for succinate, and the '249 application discloses 50 mM succinate with interferon. The Examiner has not shown that Applicants' claimed molarity range, about 10 mM to about 40 mM, overlaps with any molarity range disclosed in the prior art. Therefore, no demonstration of criticality is required. *See also* MPEP §2144.05 III (prima facie case of obviousness *based on overlapping ranges* can be rebutted by showing the criticality of the claimed range)(emphasis added).

For all of the reasons stated above, the bases for the rejection of the claims under §103 have been overcome. Applicants respectfully request that this rejection be withdrawn.

CONCLUSION

In view of the aforementioned remarks, Applicants respectfully submit that the rejections of the claims under 35 U.S.C. §112, first and second paragraphs, and §103 are overcome. Accordingly, it is submitted that this application is now in condition for allowance. Early notice to this effect is solicited.

If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

Eric J. Kron
Registration No. 45,941

Customer No. 000826
ALSTON & BIRD LLP
Bank of America Plaza
101 South Tryon Street, Suite 4000
Charlotte, NC 28280-4000
Tel Raleigh Office (919) 420-2200
Fax Raleigh Office (919) 420-2260

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, Washington, DC 20231, on December 19, 2001.

Nora C. Martinez